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Evolution and Otitis Media: A Review, and a Model to Explain High Prevalence in Indigenous Populations

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Abstract

Inflammation of the middle ear (otitis media) comprises a group of disorders that are highly prevalent in childhood, and indeed are amongst the most common disorders of childhood. Otitis media is also heritable, and has effects on fecundity. This means that otitis media is subject to evolution, yet the evolutionary selection forces that may determine susceptibility to otitis media have never been adequately explored.

Here I undertake a critical analysis of evolutionary forces that may determine susceptibility to middle ear inflammation. These forces include those determining function of the middle ear, those affecting host immunity, and those affecting colonization by, and pathogenicity of bacteria. I review existing mathematical evolutionary models of host-pathogen interaction and co-evolution, and apply these to develop a better understanding of the complex evolutionary landscape of middle ear infection and inflammation in humans. This includes an understanding of factors

determining the transition between stable evolutionary strategies for host and bacterial pathogens. This understanding will be later applied to analysis of otitis media in indigenous populations.

In the second part of this article, I apply the approach of population genetics to devise a new theory for the high prevalence of otitis media in certain indigenous populations: the Australian Aborigine, the Native American, the Inuit, and the Maori. I suggest that high prevalence in such groups may have occurred as a result of colonization of these previously isolated populations by European immigrants in the 15^{th} and 16^{th} Centuries. This exposed them to new strains of bacteria to which their immune system had not evolved immunity, perturbing a previously stable host-pathogen co-evolutionary state.

Inflammation of the middle ear is termed otitis media (OM), and is a very common affliction of childhood. OM has several phenotypes, which are inter-related (Bhutta 2014). Infection of the middle ear, is termed acute otitis media (AOM), and is the most common bacterial infection in childhood, afflicting 59% of two year old children in a developed world environment (Teele et al 1989). Other children develop persistent effusion (fluid) in the middle ear, which when lasting at least three months is termed chronic otitis media with effusion (COME). COME affects 5–6% of two-year old children in the developed world, and is the most common cause of hearing loss in children. In the developing world, many children and adults suffer from persistent infection of the ear, manifesting as purulent discharge from the ear. This is termed chronic suppurative otitis media (CSOM), and is estimated to affect 200 million people worldwide (Monasta et al 2012), with significant hearing loss in 160 million of these (Murray CJL 1996).

Otitis media is also highly heritable. Heritability of recurrent ear infections (recurrent acute otitis media, rAOM) in white infants has been estimated to be 0.49 (Rovers et al 2002). In chronic otitis media with effusion (COME), time with effusion has heritability of 0.73 (Casselbrant et al 1999). For chronic suppurative otitis media (CSOM) a study in the Inuit population reported a 2.55 odds ratio of disease in those with parental history (Jensen et al 2011).

Otitis media can also affect reproductive fitness. Current global deaths from OM (largely due to intracranial spread of infection from AOM) are estimated at 21,000 annually, and these by and large occur in early childhood (Monasta et al 2012), before reproduction has occurred. This is in the context of 709 million global cases of AOM annually (Monasta et al 2012), meaning that the calculated case fatality rate is only 0.0003%. Importantly, this is much lower than case fatality rates for other

respiratory infectious diseases: for example severe paediatric pneumonia in resource-limited settings can carry a case mortality rate as high as 10% (Enarson et al 2014). Chronic otitis media can also affect reproductive fitness, through effects on hearing due to erosion of the ossicles (middle ear bones), or by filling the middle ear with effusion. The effect of the hearing loss on reproductive fitness is difficult to quantify.

Hence, otitis media comprises a set of disorders that are common, that are highly heritable, and that can affect reproductive fitness. This set of circumstances means that susceptibility to OM will be subject to evolutionary forces. At face value, this set of circumstances may actually suggest that susceptibility to otitis media should undergo negative selection, and so become rare. This is not the case. Erosion of the temporal bone has been documented in a 40,000 year old human skull (Day 1977, Montgomery 1994), implying that morbidity and mortality from OM has featured throughout the evolutionary history of modern humans, and it is certainly still highly prevalent today.

Otitis media remains prevalent because it is a complex infectious disease. Bacteria that normally reside in the human nasopharynx are the cause of AOM, when they ascend up the Eustachian tube into the middle ear (figure 1). Chronic forms of OM are probably also a consequence of bacterial infection (Bhutta 2014). The evolutionary forces that drive human susceptibility to middle ear inflammation cannot therefore be considered in isolation, but rather exist in complex interplay with the evolutionary forces affecting colonization, survival and pathogenicity of bacteria living in the nasopharynx. The evolutionary battle between host and pathogen is a perpetual phenomenon (Karlsson et al 2014), and the continued contemporary prevalence of otitis media is testament to this fact.

In this essay I will undertake a novel analysis of the evolutionary forces at play in otitis media, and try to unpick some of the underlying complexity.Bluestone has suggested that human susceptibility to otitis media is closely related to evolution of craniofacial morphology (Daniel 1999), and in particular the angulation and calibre of the Eustachian tube (Bluestone 2008, Bluestone & Swarts 2010). These ideas are premised on the notion that anatomy or function of the Eustachian tube is the major determinant of susceptibility to OM (Bluestone 2005), but this premise is questionable, and seems insensitive to the complexities of host and pathogen interaction. There is little evidence that the Eustachian tube is in some way abnormal in the OM susceptible population: in fact most evidence suggests no difference (de Ru & Grote 2004, Sade & Ar 1997). Bluestone also suggests that otitis media is almost unique to humans (Bluestone & Swarts 2010), but actually OM is well documented by the veterinary community in small and large domestic animals, including dogs, cats, rabbits, ruminants, horses, pigs, and camelid, although it can be difficult to diagnose (Kahn & Line 2010). It seems likely that otitis media is also prevalent in non-domesticated animals.

The factors at play in the evolution and genetics of human otitis media will not be simple. They will incorporate selection pressures determining function and dysfunction of the middle ear and the host immune system, together with models of population genetics and host-pathogen interaction and co-evolution. Here I will consider these factors in turn, to build a better understanding of evolution as it pertains to middle ear inflammation. I will then integrate this analysis into a new theoretical model to understand why certain indigenous populations have a high propensity to otitis media, underlining the importance of how an understanding of

evolutionary forces can be used to understand factors determining contemporary human disease.

Evolutionary forces affecting function of the middle ear, nasopharyngeal microbiome, and host immunity

Evolution of the middle ear

When animals transitioned from an aquatic to a terrestrial existence this created a significant mismatch in sound impedance from the interface between the air-filled environment and the fluid filled inner ear. The middle ear evolved as an air-filled sound transformer to overcome this mismatch. In humans the middle ear provides up to a 27 decibel gain in hearing for air-borne sound (Kurokawa & Goode 1995). Between the Carboniferous and Triassic periods the middle ear independently evolved in five lineages—the anurans, turtles, lepidosaurs, archosaurs and mammals (Christensen-Dalsgaard & Carr 2008), and such convergent evolution is evidence of the survival advantage of an air-filled space to hearing in a terrestrial environment.

Thus, the primary function of the middle ear is to provide and maintain a gas pocket at atmospheric pressure, and even relatively minor alterations to the gaseous composition can affect hearing (Haggard 2009, Lildholdt et al 1979, Margolis et al 1994, Petrova et al 2006). Exchange of oxygen, carbon dioxide, and nitrogen between the middle ear space and venous blood occurs across the lining of the postero-superior middle ear cleft (Ars et al 1997), assisted by intermittent opening of the Eustachian tube (Adil & Poe 2014) (figure 1). Many mammals have a posterior extension of the middle ear known as the bulla, but in humans this is extensive and forms a series of interconnected air cells into the mastoid process of the temporal bone. The mastoid process probably evolved to redirect the pull of the sternocleidomastoid muscle on the

skull, to compensate for hominid adoption of an upright stance (Krantz 1963), but how and why this subsequently became pneumatised is not known. It may be that such pneumatisation increases area for gas exchange (Takahashi 2001), but why this should be necessary or advantageous in hominids is not clear.

To maintain a surface for gaseous exchange (Ar et al 2007) the middle ear is kept free of pathogens (Westerberg et al 2008) and particulate matter (and in this regard resembles the lung). Hence the antero-inferior region of the middle ear (including the Eustachian tube) is tasked with host defence (Ars & Ars-Piret 1997) and is lined with a lining that secretes and propels mucus to defend against bacterial ingress (Lim et al 2000). The normal middle ear has a paucity of white cells (Lim et al 2000) suggesting that mucus clearance alone is usually effective, despite the infant middle ear being positioned only 2cm (Ishijima et al 2000) from bacteria living in the nasopharynx.

Evolution of nasopharyngeal bacteria

Colonisation of the nasopharynx is the source of bacteria that cause AOM (Hotomi et al 2004, Tonnaer et al 2005), and therefore the initiating site for almost all OM phenotypes. Colonisation occurs rapidly after birth, and the nasopharyngeal bacterial flora is established in the first year of life (Garcia-Rodriguez & Fresnadillo Martinez 2002). By infancy the nasopharyngeal microbiome is complex and formed of an average of six million bacteria (Wilson 2005) and 20–87 different species encompassing 13 taxonomic phyla. The most common genera (figure 2) are *Moraxella, Haemophilus, Streptococcus,* and *Flavobacterium* (Bogaert et al 2011). The flora are dynamic and individualized (Bogaert et al 2011): bacterial species may be acquired, lost and re-acquired (Faden et al 1995), including through inter-species

competition (Bogaert et al 2004, Murphy et al 2009), or subject to seasonal variations (Bogaert et al 2011).

Nasopharyngeal commensal bacteria are ecotropic, site-specific, and have co-evolved with their host. The majority of commensals exist in a symbiotic, or at least tolerated relationship: they rarely cause disease, may prevent colonization with potential bacterial pathogens, and can reside in the nasopharynx of their host throughout life. In contrast some species, notably *Streptococcus pneumoniae*, non-typeable *Haemophilus influenza (*NT*Hi)*, or *Moraxella catarrhalis*, do have pathogenic potential. Exposure to new strains of these bacteria can result in clearance, asymptomatic colonization (Faden et al 1991, Prellner et al 1984a), or respiratory tract infection, including AOM (Faden et al 1997, Gray et al 1980), but also rhinosinusitis (Brook & Gober 2007) or pneumonia (Hausdorff & Dagan 2008). Such disease usually occurs following viral URTI (Bhutta 2014), suggesting virulent bacteria and upper respiratory tract viruses have likely co-evolved. Mechanisms of viral-bacterial co-evolution have not been explored. No particular virus appears to synergise with any bacterial strain (Alper et al 2009), and there appears to be convergent evolution, in that viruses use species-specific mechanisms for synergistic bacterial infection (Avadhanula et al 2006), which may include promotion of bacterial adhesion, disruption of the epithelial barrier, and interference with the host immune system (Bosch et al 2013). Perhaps synergism allows viral and bacterial species to together seize an opportunity to overwhelm the host immune system and so expand their populations. Synergism could also be to capitalise on symptoms such as cough, which can be invoked by viruses (Footitt & Johnston 2009) and possibly also bacteria (Gunnarsson et al 2000), or sneezing, which generate bioaerosols and so enhance pathogen spread (Fiegel et al 2006).

Bacteria that colonise the human nasopharynx seem to have adopted strategies of either virulence or avirulence, and mathematical models (Boots et al 2009, Miller et al 2005) predict these two outcomes to be co-evolutionary stable states. Avirulence will likely lead to host tolerance and long-term carriage, thus favouring microbe spread between hosts over prolonged periods. Virulence enables massive bacterial population expansion during the pathogenic phase, thus promoting spread between susceptible hosts (which in the case of AOM will largely be infants that naturally are relatively immunodeficient), but with the disadvantage that colonization may be only short-term if (when) the host generates an immune response sufficient for eradication. The major otopathogens *S. pneumoniae*, NT*Hi*, or *M. catarrhalis* can often be cultured from the nasopharynx of infants, but are rarely found in adults (Garcia-Rodriguez & Fresnadillo Martinez 2002, Gunnarsson et al 1998), and I suggest this is because immune response in the host leads to their eventual clearance, although formation of a bacterial biofilm (Murphy et al 2009) may afford some protection.

Advances in genetic sequencing have provided further insight into the transition between evolutionary strategies for the nasopharyngeal microbiome. For example *M. cattarhalis* probably attained virulence coincident with, and as a consequence of, human population expansion (Wirth et al 2007), although the molecular mechanisms are unclear (Davie et al 2011). Sequencing data suggests that *Streptococcus pneumoniae* evolved as a derivative of the commensal species *Streptococcus mitis*, through horizontal gene transfer that enabled a diverse structure to its cellular wall, creating bacterial virulence (Kilian et al 2008, Kilian et al 2014). The evolutionary history of *Haemophilus influenzae* is not well understood (Maughan & Redfield 2009). Of course, these strategies are not mutually exclusive. Not all colonization with *S. pneumoniae*, NT*Hi*, or *M. cattarhalis* leads to disease, and

commensals like *Fusobacterium necrophorum* or group A streptococci that are normally avirulent can occasionally be pathogenic and cause otitis media (Le Monnier et al 2008, Turner et al 2002). Indeed the evolutionary dynamics will be affected by many factors, including pathogen transmission rates and risk of mortality (Hoyle et al 2008) but also, and importantly, host population ecology (Frank 1991). In particular, existing computer modeling suggests that expanding host populations favour pathogen virulence, whereas stable or declining populations favour avirulence.

Evolution of host immune response

The ontogeny and phylogeny of the immune system is from mucosal epithelium (Drayton et al 2006), reflecting that this is the entry point for most infectious agents (Murphy et al 2008). The mucosa associated lymphatic tissue (MALT) contains 80% of all immunocytes, is separate in structure and function from the systemic immune system, and is compartmentalised into gut-associated lymphatic tissue (GALT) and nasal associated lymphatic tissue (NALT) (Holmgren & Czerkinsky 2005).

Infectious disease is a major driver of evolution (Karlsson et al 2014), and given the morbidity and mortality of respiratory infections (Schluger 2010), function of NALT will have been, and continue to be, subject to major evolutionary pressure. However, mucosal immune regulation remains poorly understood, and in particular the mechanisms that determine tolerance versus an active immune response—although secretory immunoglobulin A appears to play an important role (Strugnell & Wijburg 2010).

NALT in humans is particularly well developed in comparison to other mammals such as rodents, and is arranged as lymphoid aggregates that form a ring (Waldeyer's ring) at the inlet to the pharynx/throat (figure 3) (Brandtzaeg 2003). This

development perhaps reflects the fact that humans are a societal species, with high exposure to air-borne microorganisms through social contact. Importantly, NALT is embryologically and functionally distinct from GALT (Kiyono & Fukuyama 2004, Ruddle & Akirav 2009), evidencing that it has been subject to site-specific evolutionary forces (Wu & Russell 1997). Empirically, this suggests that upstream regulators of the immune response in NALT have also evolved to be site-specific, although downstream (phylogenetically ancient) signaling may utilise pathways in common with the rest of the immune system. Evidence from other contexts reveals wide variation in immune function in different tissue types (Matzinger & Kamala 2011). The components of different tissues that determine this variation in immune function are not well understood, but seem important.

A priori it may appear that the host population should be constantly striving to win the arms race against potentially pathogenic microorganisms, but this is not necessarily true. The immune system consumes significant energy capital (Muehlenbein et al 2010), and so the usage costs (and risks of morbidity and mortality) of fighting an infection are balanced by the resource investment required to maintain an immune system (Sheldon & Verhulst 1996). In addition, because pathogens usually have a shorter generation time and larger population size than their hosts, they are more adaptable, and so the host may never completely win this battle (Schulenburg et al 2009). Population models suggest that for species such as humans, that are long-lived and utilise acquired immunity, the optimum evolutionary strategy may be to allow the occasional infection (Schmid-Hempel 2003). If the host survives the infection, acquired immunity will prevent similar infection in the future, but the pre-programmed lower basal investment in immune maintenance may increase fecundity over the lifetime of the individual. The optimum strategy will vary with host

and population dynamics, thus engendering intra-species diversification, and genotypic variation with regard to host immune response (Miller et al 2007).

Prolonged (chronic) inflammatory response may occur as a result of persistent antigenic stimulation, but may also be pre-programmed, for example as a strategy to enhance clearance of antigens (Caruso et al 2004). There is evidence that human evolution has favoured a more pro-inflammatory genotype when compared to other primates, perhaps to enhance pathogen clearance, and thus engender longevity of our species (Finch 2010) and the unique system of multigenerational support in child nurture that this affords (Hawkes 2004). However, chronic inflammation can be maladaptive (Medzhitov 2008), and risks causing irreparable tissue damage (Karin et al 2006). Pro-inflammatory genotypes exemplify antagonistic pleoitropy (Leroi et al 2005), whereby a polymorphism may serve a useful function in the short term but have negative consequences in the longer term.

The Genetic Landscape of Otitis Media

We can apply some of the broad principles of population genetics to understand the genetic landscape of otitis media.

Susceptibility to rAOM

Importantly, the phenome of susceptibility to rAOM includes susceptibility to other respiratory tract infections, including tonsillitis (Kvaerner et al 1996, Kvestad et al 2006), rhinosinusitis (Kvaerner et al 1996), and bronchopulmonary infections (Stenstrom & Ingvarsson 1994), and, to a lesser extent, susceptibility to extra-respiratory mucosal infections (Stenstrom & Ingvarsson 1994). The association with bronchopulmonary infections occurs because AOM and most lower respiratory tract

infections (LRTI) are alternate (or common) outcomes of nasopharyngeal colonization by the same species of respiratory pathogens. Because mortality due to LRTI (Schluger 2010) is more prevalent than that due to intracranial spread of middle ear infection (Monasta et al 2012, WHO 2004), prevention of LRTI will likely be the main determinant of host investment in NALT immune function. The lower respiratory tract is also likely to be the preferred site for infection by pathogenic bacteria; LRTI aids bioaerosol dispersion, but there is relatively little to be gained for the pathogen through infection of the middle ear space. Thus, the middle ear may be an unfortunate bystander in the battle of host versus respiratory pathogen. The middle ear is susceptible to infection, yet exerts comparatively little evolutionary pressure to prevent such infection.

The high heritability of rAOM implies that host response is the main determinant of disease susceptibility, specifically NALT immune response to potentially virulent infectious agents (Faden 2001, Garcia-Rodriguez & Fresnadillo Martinez 2002, Rynnel-Dagoo & Agren 2000). Some evidence supports this notion. First the pathogens causing rAOM are the same as those causing AOM (Pichichero 2000), but children prone to rAOM experience nasopharyngeal bacterial colonisation more frequently (Faden et al 1991, Harabuchi et al 1994) and with higher density (Stenfors & Raisanen 1992), although this may also be found in children with COME (Marchisio et al 2003)). Quantitative or qualitative defects in plasma immunoglobulins have been found in some, but not all, of those with rAOM (Freijd et al 1984, Freijd et al 1985, Harsten et al 1989, Hotomi et al 1999, Prellner et al 1984b, Stenfors & Raisanen 1993, Yamanaka & Faden 1993).

Extrapolation from other infectious diseases suggests that susceptibility to rAOM will likely factor a very large number of genes (Burgner et al 2006). The arms

race between pathogen and host has engendered a complex immunological network of pathogen recognition and signaling molecules in the host, and with considerable redundancy (Nish & Medzhitov 2011). Susceptibility loci may encompass those determining bacterial adhesion, mucociliary clearance, innate immune response, or adaptive immune response, and may be those regulating such functions throughout the mucosa, or more specifically only in nasopharyngeal mucosa. We still know relatively little about human genetic susceptibility to rAOM (Rye et al 2012).

Susceptibility to COME

For chronic otitis media, we may hypothesise from evolutionary theory (Medzhitov 2008) that because persistent middle ear inflammation is common it must have at least some beneficial effect (Cochran et al 2000). Empirically, this inflammation could aim to enhance clearance of, or prevent proliferation of, microorganisms (de Ru & Grote 2004), and there is evidence to support this idea. Bacterial mRNA can be detected in 37–94% of effusions in COME (Calhoun et al 1988, Giebink et al 1982, Gok et al 2001, Hendolin et al 1997, Liu et al 1976, Liu et al 1975, Palva et al 1983, Park et al 2004), suggesting that metabolically active bacteria are present, but are constrained in their proliferation. Indeed, the effusion in OME has been shown to be bacteriostatic (Siirala 1952) and bactericidal (Shimizu et al 1988), presumably due to the mucins, immunoglobulins, and cytokines within the effusion. The viability of bacteria in effusions negatively correlates to the levels of such constituents (Lang et al 1976, Lim et al 1979, Liu et al 1976). There is a (small) increase in AOM following insertion of ventilation tubes for COME (which removes the effusion), which further evidences potential anti-bacterial effects of the effusion (Ingels et al 2005) (although very few

studies of ventilation tubes have specifically looked at this outcome (Browning et al 2010, Rosenfeld 2000)).

The reverse hypothesis has also been advanced, that the effusion in OME provides the milieu for increased bacterial colonization, and so contributes to AOM. It is true that AOM can be immediately preceded by OME, but this may reflect the imperfection of a sero-mucoid effusion in its attempt to prevent suppuration, rather than implying that it contributes to that suppuration. With rAOM, the common observation that OME is also present may represent recurrent rather than chronic OME.

Whereas protection against microorganisms may possibly be the advantage, and possibly the evolutionary purpose of chronic otitis media, clearly prolonged inflammation can also be detrimental. Prolonged effusion in COME creates an air-fluid interface that prevents the transmission of sound, and thus counteracts the purpose of the middle ear. The consequential hearing loss could reduce audition of danger but the handicap will be somewhat ameliorated, at least during infancy, by the long parent-child bond in our species. Reduced hearing can also interfere with language acquisition, although the long-term consequences of COME on linguistic abilities are debated (Roberts et al 2004). Consequently chronic inflammation of the ear in infancy may have relatively little effect on fecundity, and there may be little evolutionary pressure to select against it. In the longer-term middle ear fibrosis, tympanic retraction, chronic otorrhoea, or erosion of the bones of hearing can lead to irreversible hearing loss, but these consequences are relatively rare and may be offset by any potential advantage of chronic inflammation in earlier life.

Pathways driving chronicity of inflammation are not well understood. It is not known to what extent chronic inflammation results from a failure of catabolism of

pro-inflammatory mediators, and to what extent it may be a failure of induction of pro-resolution programs (Serhan et al 2007). Nor do we know the relative roles of leucocytes, stromal cells or mucosal cells in this process. Whereas the acute inflammatory response invokes a very large number of pathways, and with redundancy, empirically it is plausible that a smaller number of pathways are involved in driving chronicity of inflammation. Indeed homozygous polymorphisms in acute inflammatory response genes rarely cause a significant phenotype, whereas similar polymorphisms in key regulators of inflammation can lead to chronic inflammation (Wells et al 2005).

Chronic OM is not knowingly associated with chronic inflammation in extra-tympanic sites, in childhood nor in later life (but this question has never been adequately investigated). Given the development of site-specificity of immune response in latter phlylogeny, and the lack of evidence of extra-tympanic inflammation, it may be that susceptibility to chronic middle ear inflammation is determined by only a handful of genes that function as locoregional regulators of inflammation.

Ethnic variations in otitis media incidence

The earlier analysis and understanding of the complex forces at play in otitis media susceptibility can be used to understand why certain populations are more susceptible to otitis media.

A number of studies have reported differences in prevalence of otitis media by ethnicity. These differences could be due to ethnic variations in socio-economic factors (Vernacchio et al 2004) or in illness-seeking behavior (Park et al 2002), as well as genetics, but because many studies have been retrospective they have been

unable to control for such confounders. Furthermore studies have been contradictory, and the conclusions of systematic (Smith & Boss 2010) and narrative (Bluestone 2005, Bluestone & Klein 2007, Casselbrant 2003) reviews do not agree on differences in OM prevalence between white, black, Hispanic or Asian children in the developed world. In the developing world only CSOM has been studied in any detail, but methodological differences and inconsistent disease definition make it difficult to compare reported geographical variations in prevalence (Monasta et al 2012, WHO 2004).

However, there are reliable data that show a high prevalence of otitis media in children of the indigenous Inuit (Curns et al 2002, Ling et al 1969, Maynard et al 1972, Pedersen & Zachau-Christiansen 1986, Reed et al 1967, Singleton et al 2009), Native American (Curns et al 2002, Maynard et al 1972, Singleton et al 2009, Zonis 1968), Maori (Giles & Asher 1991, Gribben et al 2012, Hamilton et al 1980, Stanhope et al 1978), or Australian Aborigine (Boswell & Nienhuys 1995, Gunasekera et al 2007, Morris et al 2005, Williams et al 2009) populations when compared to white conspecifics. These indigenous groups seem more susceptible to both AOM and CSOM (table). Socioeconomic disparities may contribute to this difference, but the incidence of OM in indigenous groups is exceptionally high, suggesting that genetic differences are likely to be important.

It has been mooted that anatomical factors in Eustachian tube morphology or in middle ear anatomy may underlie ethnic variation in OM incidence, but data to support this theory are weak (Beery et al 1980, Bluestone 2005, Jassar et al 2006, Wiet et al 1982). Craniofacial differences in human populations appear to have arisen largely as a consequence of genetic drift (Betti et al 2010), rather than evolutionary pressures. Because of the current lack of good evidence that a particular craniofacial

form is responsible for ethnic variations in OM susceptibility, theories based on this premise seem weak. They also seem undermined by the fact that these ethnic groups listed above are not particularly closely related. Thus, I feel alternative explanations should be considered.

Here, I present an alternative hypothesis, based upon population genetics and phylogeography. Prior to European exploration and colonization in the late 15th and 16th Centuries (figure 4), the Eurasian and African populations numbered in the hundreds of millions, and were sympatric (they probably interbred until 20–40,000 years ago, (Li & Durbin 2011). Thus, it seems likely that microorganisms would have spread across the African and Eurasian populations, aided by regional and inter-continental trade, and (for respiratory microorganisms) by wind. In comparison, the Inuit, Native American, Maori, and Australian Aboriginal populations at this time had relatively small total and demic population sizes, and each of these populations lived in relative geographic and social isolation. Hence, for the large part they were exposed only to local or regional microorganisms. In addition, indigenous populations had experienced repeated population bottlenecks (Manica et al 2007), which had reduced the genetic diversity in these isolated groups (Mulligan et al 2004) compared to Eurasian or African conspecifics (DeGiorgio et al 2009). The effect of these bottlenecks on associated microbial diversity is not well known.

Given that the Inuit, Native American, Maori or Australian Aborigine populations were largely separated from Eurasian and African populations for a period of 30–45,000 years, we would expect these groups to have diverged through genetic drift. Similarly we would expect drift to lead to geographic divergence in the nasopharyngeal microbiome. Hence empirically, due to co-evolution between human and microorganism, evolutionary stable strategies will invoke different loci (in host

and pathogen) in geographically isolated populations, and the nature of the strategy likely will vary with local host population size and dynamics. In particular, large and expanding populations, such as the European population, favour higher virulence in microorganisms, whereas smaller populations sizes, such as the Inuit, North American, Maori, or Australian Aborigine, tend to favour less virulent strains (Real & Biek 2007). With the advent of European world exploration in the 15th Century, indigenous populations became exposed to virulent respiratory microorganisms co-evolved with Europeans, to which they had not evolved specific immunity.

There is (indirect) evidence in support of this hypothesis. Population genetics modeling confirms predicted divergence of host-pathogen co-evolutionary strategy in allopatric populations (Best et al 2011). Indeed sampling of flora in sites such as the oral cavity (Caufield 2009) or stomach (Linz et al 2007, Yamaoka 2009) confirms geographic variations in bacterial genotype (Wirth et al 2005). Similarly, allele frequencies in immunomodulatory loci have been found to differ between ethnic groups (Van Dyke et al 2009) (although the functional effect of these variations is not well understood). Furthermore, population genetics predicts potential catastrophic infectious disease from the coalescence of groups that historically have been spatially segregated (Best et al 2011). History documents this effect, whereby Old World diseases such as smallpox and measles introduced by colonisation of the New World were responsible for the decimation of biologically naïve native populations. Importantly, accounts from the time suggest that a similar effect occurred even with pathogens to which these populations were not entirely naïve.

To find evidence of this effect for otitis media is more difficult. Middle ear disease is not documented in historical records from the time of European colonisation. However, suppurative OM can arrest pneumatisation of the mastoid

bone, and archaeological evidence in ancient fossilized skulls of both the native American (Gregg & Steele 1982) and the Greenland Inuit (Homoe et al 1996a) does suggest an increase in OM subsequent to European colonisation. Genetic variation in the nasopharyngeal flora by ethnic groups has not been studied, either in contemporary or bioarchaeological remains, but the nasopharynx of Australian Aborigine children is known to be colonized by potential otopathogens at an earlier age (Leach et al 1994) and in higher numbers (Watson et al 2006), and this is predictive of subsequent middle ear suppuration (Smith-Vaughan et al 2006). This supports the idea that Aborigine populations are colonised by variants of nasopharyngeal commensals with which they have not co-evolved, and to which they may not have the genetic repertoire to mount a directed and specific immune response. More frequent and more dense nasopharyngeal colonisation by otopathogens has also been documented in the Inuit (Homoe et al 1996b).

If nasopharyngeal host-pathogen co-evolution is responsible for ethnic variations in OM, we would predict variation in susceptibility to other respiratory infections. Indeed epidemiological studies show that childhood LRTI is highly prevalent in the Inuit (Banerji et al 2001, Banerji et al 2009, Koch et al 2002, Young et al 2007), native American (Bockova et al 2002, Holman et al 2004, Lowther et al 2000, Meissner 2003, Peck et al 2005), Maori (Grant et al 1998, Grimwood et al 2008, Tukuitonga et al 2000), and Aborigine populations (Carville et al 2007, Dede et al 2010, Gracey et al 1992, Moore et al 2007, Read et al 1996, Williams et al 1997). An obvious confounder for this association is that many of these indigenous populations also suffer lower socio-economic status, which will also increase their risk of infectious disease. However, most of these epidemiological studies have

controlled for variation in socio-economic status, and found that prevalence remains high even after such control.

The confluence of populations disparate in their genetics and microbiology may not be the only relevant change to occur following European colonization of indigenous groups. Prior to European contact many indigenous groups lived in small groups and often with a nomadic lifestyle, whereas following colonization many lived in larger groups in a fixed abode. Such changes to the structure of indigenous societies can also have important effects on host-pathogen dynamics.

Future studies to support the hypothesis presented here could look to evaluate strain and substrain variation in the nasopharyngeal microbiome in indigenous populations compared to non-indigenous populations. However, I recognise that results may be compounded by the fact that many indigenous and non-indigenous populations are now in regular contact, meaning that they may share a microbiome in common. Studies on (rare) human populations that still live in relative isolation may be another way to answer this question.

Conclusion

Otiis media has been prevalent throughout the history of modern humans, and is subjective to evolutionary selection pressure. Forces at interplay in the evolution of otitis media have been explored here, and include those affecting middle ear function, colonization of the nasopharynx by potential pathogens, and host immunity. The ecology of human populations is predicted to play a strong role in determining the evolutionarily stable state with regards to otitis media, and disruption of this ecology by European colonization may explain the contemporary high prevalence of otitis media in previously isolated indigenous populations.

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Literature Cited

Adil, E., D. Poe. 2014. What is the full range of medical and surgical treatments available for patients with Eustachian tube dysfunction? *Curr. Opin. Otolaryngo.* 22: 8–15.

Alper, C. M., B. Winther, E. M. Mandel et al. 2009. Rate of concurrent otitis media in upper respiratory tract infections with specific viruses. *Arch. Otolaryngol.* 135: 17–21.

Ar, A., P. Herman, E. Lecain et al. 2007. Middle ear gas loss in inflammatory conditions: the role of mucosa thickness and blood flow. *Respir. Physiol. Neurobiol.* 155: 167–76.

Ars, B. and N. Ars-Piret. 1997. Morpho-functional partition of the middle ear cleft. *Acta. Otorhinolaryngol. Belg* 51: 181–4.

Ars, B., F. Wuyts, P. Van de Heyning et al. 1997. Histomorphometric study of the normal middle ear mucosa. Preliminary results supporting the gas-exchange function in the postero-superior part of the middle ear cleft. *Acta Oto-laryngol.* 117: 704–7.

Avadhanula, V., C. A. Rodriguez, J. P. Devincenzo et al. 2006. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. *J. Virol.* 80: 1629–36

Banerji, A., A. Bell, E. L. Mills et al. 2001. Lower respiratory tract infections in Inuit infants on Baffin Island. *CMAJ* 164: 1847–50.

Banerji, A., D. Greenberg, L. F. White et al. 2009. Risk factors and viruses associated with hospitalization due to lower respiratory tract infections in Canadian Inuit children : a case-control study. *Pediatr. Infect. Dis. J.* 28: 697–701.

Beery, Q. C., W. J. Doyle, E. I. Cantekin et al. 1980. Eustachian tube function in an American Indian population. *Ann. Otol. Rhinol. Laryngol. Suppl.* 89: 28–33

Best, A., S. Webb, A. White et al. 2011. Host resistance and coevolution in spatially structured populations. *Proc. Biol. Sci.* 278: 2216–22.

Betti, L., F. Balloux, T. Hanihara, and A. Manica. 2010. The relative role of drift and selection in shaping the human skull. *Am. J. Phys. Anthropol.* 141: 76–82.

Bhutta, M. F. 2014. Epidemiology and pathogenesis of otitis media: construction of a phenotype landscape. *Audiol. Neurootol.* 19: 210–23.

Bluestone, C. D. 2008. Impact of evolution on the eustachian tube. *The Laryngoscope* 118: 522–7.

Bluestone, C. D., M. B. Bluestone, J. Coulter. 2005. *The Eustachian Tube: Structure, Function, Role in Otitis Media*. Hamilton: B C Decker.

Bluestone, C. D., J. O. Klein. 2007. *Otitis Media in Infants and Children*. Hamilton: B C Decker.

Bluestone, C. D., J. D. Swarts. 2010. Human evolutionary history: consequences for the pathogenesis of otitis media. *Otolanryng. Head. Neck.* 143: 739–44.

Bockova, J., K. L. O'Brien, J. Oski et al. 2002. Respiratory syncytial virus infection in Navajo and White Mountain Apache children. *Pediatrics* 110: e20.

Bogaert, D., R. De Groot, P. W. Hermans. 2004. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet. Infect. Dis.* 4: 144–54.

Bogaert, D., B. Keijser, S. Huse et al. 2011. Variability and diversity of nasopharyngeal microbiota in children: a metagenomic analysis. *PloS one* 6: e17035.

Boots, M., A. Best, M. R. Miller et al. 2009. The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 364: 27–36.

Bosch, A. A., G. Biesbroek, K. Trzcinski et al. 2013. Viral and bacterial interactions in the upper respiratory tract. *PLoS Pathog.* 9: e1003057.

Boswell, J. B., T. G. Nienhuys. 1995. Onset of otitis media in the first eight weeks of life in aboriginal and non-aboriginal Australian infants. *Ann. Oto. Rhinol. Laryn.* 104: 542–9.

Brandtzaeg, P. 2003. Immunology of tonsils and adenoids: everything the ENT surgeon needs to know. *Int. J. Pediatr. Otorhi.* 67 Suppl 1: S69–76.

Brook, I., A. E. Gober. 2007. Frequency of recovery of pathogens from the nasopharynx of children with acute maxillary sinusitis before and after the introduction of vaccination with the 7-valent pneumococcal vaccine. *Int. J. Pediatr. Otorhi.* 71: 575–9.

Browning, G. G., M. M. Rovers, I. Williamson et al. 2010. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. *Cochrane Db. Syst. Rev*. CD001801.

Burgner, D., S. E. Jamieson, J. M. Blackwell. 2006. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? *Lancet Infect. Dis.* 6: 653–63.

Calhoun, K. H., W. B. Norris, J. A. Hokanson et al. 1988. Bacteriology of middle ear effusions. *South. Med. J.* 81: 332–6.

Caruso, C., D. Lio, L. Cavallone et al. 2004. Aging, longevity, inflammation, and cancer. *Ann. N. Y. Acad. Sci.* 1028: 1–13.

Carville, K. S., D. Lehmann, G. Hall et al. 2007. Infection is the major component of the disease burden in aboriginal and non-aboriginal Australian children: a population-based study. *Pediatr. Infect. Dis. J.* 26: 210–6.

Casselbrant, M. L. 2003. Epidemiology In *Evidence-Based Otitis Media*, ed. RM Rosenfeld, Bluestone C.D., pp. 147–62. Hamilton: B C Decker.

Casselbrant, M. L., E. M. Mandel, P. A. Fall et al. 1999. The heritability of otitis media: a twin and triplet study. *JAMA* 282: 2125–30.

Caufield, P. W. 2009. Tracking human migration patterns through the oral bacterial flora. *Clin. Microbiol. Infect.* 15 Suppl 1: 37–9.

Chen Y, Tran C. 2011. *Toronto Notes*. Maidenhead: McGraw Hill.

Christensen-Dalsgaard, J., C. E. Carr. 2008. Evolution of a sensory novelty: tympanic ears and the associated neural processing. *Brain Res. Bull*. 75: 365–70.

Cochran, G. M., P. W. Ewald, K. D. Cochran. 2000. Infectious causation of disease: an evolutionary perspective. *Perspect. Biol. Med.* 43: 406–48.

Curns, A. T., R. C. Holman, D. K. Shay et al. 2002. Outpatient and hospital visits associated with otitis media among American Indian and Alaska native children younger than 5 years. *Pediatrics* 109: E41–1.

Daniel, H. J. 1999. Otitis media: an evolutionary perspective In *Evolutionary Medicine*, ed. W Trevathan, EO Smith, JJ McKenna, pp. 75–100. New York: Oxford University Press.

Davie, J. J, J. Earl, S. P. de Vries et al. 2011. Comparative analysis and supragenome modeling of twelve Moraxella catarrhalis clinical isolates. *BMC Genomics* 12: 70.

Day, M. H. 1977. *Guide to fossil man*. London: Cassell.

de Ru, J. A., J. J. Grote. 2004. Otitis media with effusion: disease or defense? A review of the literature. *Int. J. Pediatr. Otorhi.* 68: 331–9.

Dede, A., D. Isaacs, P. J. Torzillo et al. 2010. Respiratory syncytial virus infections in Central Australia. *J. Paediatr. Child. Health.* 46: 35–9.

DeGiorgio, M., M. Jakobsson, N. A. Rosenberg. 2009. Out of Africa: modern human origins special feature: explaining worldwide patterns of human genetic variation using a coalescent-based serial founder model of migration outward from Africa. *Proc. Natl. Acad. Sci. USA* 106: 16057–62.

Drayton, D.L., S. Liao, R. H. Mounzer et al. 2006. Lymphoid organ development: from ontogeny to neogenesis. *Nat. Immunol.* 7: 344–53.

Enarson, P.M., R. P. Gie, C. C. Mwansambo et al. 2014. Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management. *PloS one* 9: e102955.

Faden, H. 2001. The microbiologic and immunologic basis for recurrent otitis media in children. *Eur. J. Pediatr.* 160: 407–13.

Faden, H., L. Duffy, R. Wasielewski et al. 1997. Relationship between nasopharyngeal colonization and the development of otitis media in children. Tonawanda/Williamsville Pediatrics. *J. Infect. Dis.* 175: 1440–5.

Faden, H., L. Duffy, A. Williams et al 1995. Epidemiology of nasopharyngeal colonization with nontypeable Haemophilus influenzae in the first 2 years of life. *J. Infect. Dis.* 172: 132–5.

Faden, H., M. J. Waz, J. M. Bernstein et al. 1991. Nasopharyngeal flora in the first three years of life in normal and otitis-prone children. *Ann. Oto. Rhinol. Laryn.* 100: 612–5.

Fiegel, J., R. Clarke, D. A. Edwards. 2006. Airborne infectious disease and the suppression of pulmonary bioaerosols. *Drug Discov. Today* 11: 51–7.

Finch, C. E. 2010. Evolution in health and medicine Sackler colloquium: Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. *Proc. Natl. Acad. Sci. USA* 107 Suppl 1: 1718–24.

Footitt, J., S. L. Johnston. 2009. Cough and viruses in airways disease: mechanisms. *Pulm. Pharmacol. Ther.* 22: 108–13.

Frank, S. A. 1991. Ecological and genetic models of host-pathogen coevolution. *Heredity* 67 (Pt 1): 73–83.

Freijd, A., L. Hammarstrom, M. A. Persson et al. 1984. Plasma anti-pneumococcal antibody activity of the IgG class and subclasses in otitis prone children. *Clin. Exp. Immunol.* 56: 233–8.

Freijd, A., V. A. Oxelius, B. Rynnel-Dagoo. 1985. A prospective study demonstrating an association between plasma IgG2 concentrations and susceptibility to otitis media in children. *Scand. J. Infect. Dis.* 17: 115–20.

Garcia-Rodriguez, J. A., M. J. Fresnadillo Martinez. 2002. Dynamics of nasopharyngeal colonization by potential respiratory pathogens. *J. Antimicrob. Chemother.* 50 Suppl S2: 59–73.

Gibbard, P., T. van Kolfschoten. 2004. The Pleistocene and Holocene Epochs In *A Geologic Time Scale*, ed. UoC Quaternary Palaeoenvironments Group. Cambridge: Cambridge University Press.

Giebink, G. S., S. K. Juhn, M. L. Weber et al. 1982. The bacteriology and cytology of chronic otitis media with effusion. *Pediatr. Infect. Dis.* 1: 98–103.

Giles, M., I. Asher. 1991. Prevalence and natural history of otitis media with perforation in Maori school children. *J. Laryngol. Otol.* 105: 257–60.

Gok, U., Y. Bulut, E. Keles et al. 2001. Bacteriological and PCR analysis of clinical material aspirated from otitis media with effusions. *Int. J. Pediatr. Otorhi.* 60: 49–54.

Gracey, M., M. Dennison, V. Burke. 1992. Hospital admissions of Aborigines and non-Aborigines in Western Australia, 1977–1988. *Trans. R. Soc. Trop. Med. Hyg.* 86: 694–7.

Grant, C. C., R. Scragg, D. Tan et al. 1998. Hospitalization for pneumonia in children in Auckland, New Zealand. *J. Paediatr. Child Health* 34: 355–9.

Gray, B. M., G. M. Converse 3rd et al. 1980. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. *J. Infect. Dis.* 142: 923–33.

Gregg, J. B., J. P. Steele. 1982. Mastoid development in ancient and modern populations. A longitudinal radiological study. *JAMA* 248: 459–64.

Gribben, B., L. J. Salkeld, S. Hoare et al. 2012. The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting. *J. Primary Health Care* 4: 205–12.

Grimwood, K., C. Cohet, F. J. Rich et al. 2008. Risk factors for respiratory syncytial virus bronchiolitis hospital admission in New Zealand. *Epidemiol. Infect.* 136: 1333–41.

Gunasekera, H., S. Knox, P. Morris et al. 2007. The spectrum and management of otitis media in Australian indigenous and nonindigenous children: a national study. *Pediatr. Infect. Dis. J.* 26: 689–92.

Gunnarsson R. K., S. E. Holm, M. Soderstrom. 1998. The prevalence of potential pathogenic bacteria in nasopharyngeal samples from healthy children and adults. *Scand J Prim Health Care* 16: 13–7

Gunnarsson, R. K., S. E. Holm, M. Soderstrom. 2000. The prevalence of potentially pathogenic bacteria in nasopharyngeal samples from individuals with a long-standing cough-clinical value of a nasopharyngeal sample. *Fam. Pract.* 17: 150–5.

Haggard, M. 2009. Air-conduction estimated from tympanometry (ACET): 2. The use of hearing level-ACET discrepancy (HAD) to determine appropriate use of bone-conduction tests in identifying permanent and mixed impairments. *Int. J. Pediatr. Otorhi.* 73: 43–55.

Hamilton, M. A., M. McKenzie-Pollock, M. E. Heath. 1980. Aural health in 227 Northland school and preschool children. *N. Z. Med. J.* 91: 59–62.

Harabuchi, Y., H. Faden, N. Yamanaka et al. 1994. Nasopharyngeal colonization with nontypeable Haemophilus influenzae and recurrent otitis media. Tonawanda/Williamsville Pediatrics. *J. Infect. Dis.* 170: 862–6.

Harsten, G., K. Prellner, J. Heldrup et al. 1989. Recurrent acute otitis media. A prospective study of children during the first three years of life. *Acta Oto-laryngol.* 107: 111–9.

Hausdorff, W. P., R. Dagan. 2008. Serotypes and pathogens in paediatric pneumonia. *Vaccine* 26 Suppl 2: B19–23.

Hawkes, K. 2004. Human longevity: the grandmother effect. *Nature* 428: 128–9.

Hendolin, P. H., A. Markkanen, J. Ylikoski et al. 1997. Use of multiplex PCR for simultaneous detection of four bacterial species in middle ear effusions. *J. Clin. Microbiol.* 35: 2854–8.

Holman, R. C., A. T. Curns, J. E. Cheek et al. 2004. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. *Pediatrics* 114: e437–44.

Holmgren, J., C. Czerkinsky. 2005. Mucosal immunity and vaccines. *Nat. Med.* 11: S45–53.

Homoe, P., N. Lynnerup, L. T. Skovgaard et al. 1996a. Estimation of otitis media in ancient populations. A study of past and present Greenlandic Inuit. *J. Laryngol. Otol.* 110: 1114–9

Homoe, P., J. Prag, S. Farholt et al. 1996b. High rate of nasopharyngeal carriage of potential pathogens among children in Greenland: results of a clinical survey of middle-ear disease. *Clin. Infect. Dis.* 23: 1081–90.

Hotomi, M., N. Yamanaka, D. S. Billal et al. 2004. Genotyping of Streptococcus pneumoniae and Haemophilus influenzae isolated from paired middle ear fluid and nasopharynx by pulsed-field gel electrophoresis. *ORL J. Oto-Rhino-Lary.* 66: 233–40.

Hotomi, M., N. Yamanaka, T. Saito et al. 1999. Antibody responses to the outer membrane protein P6 of non-typeable Haemophilus influenzae and pneumococcal capsular polysaccharides in otitis-prone children. *Acta Oto-laryngol.* 119: 703–7.

Hoyle, A., R. G. Bowers, A. White et al. 2008. The influence of trade-off shape on evolutionary behaviour in classical ecological scenarios. *J. Theor. Biol.* 250: 498–511.

Ingels, K., M. M. Rovers, G. J. van der Wilt et al. 2005. Ventilation tubes in infants increase the risk of otorrhoea and antibiotic usage. *B-ENT* 1: 173–6.

Ishijima, K., I. Sando, C. Balaban et al. 2000. Length of the eustachian tube and its postnatal development: computer-aided three-dimensional reconstruction and measurement study. *Ann. Oto. Rhinol. Laryn.* 109: 542–8.

Jassar, P., P. Murray, D. Wabnitz et al. 2006. The posterior attic: An observational study of aboriginal Australians with chronic otitis media (COM) and a theory relating to the low incidence of cholesteatomatous otitis media versus the high rate of mucosal otitis media. *Int. J. Pediatr. Otorhi.* 70: 1165–7.

Jensen, R. G., P. Homoe, M. Andersson et al. 2011. Long-term follow-up of chronic suppurative otitis media in a high-risk children cohort. *Int. J. Pediatr. Otorhi.* 75: 948–54.

Jervis-Bardy, J., L. Sanchez, A. S. Carney. 2014. Otitis media in Indigenous Australian children: review of epidemiology and risk factors. *J. Laryngol. Otol.* 128 Suppl 1: S16–27.

Kahn, C.M., S. Line. 2010. *The Merck Veterinary Manual*. New Jersey: Merck.

Karin, M., T. Lawrence, V. Nizet. 2006. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 124: 823–35.

Karlsson, E. K., D. P. Kwiatkowski, P. C. Sabeti. 2014. Natural selection and infectious disease in human populations. *Nat. Rev. Genet.* 15: 379–93.

Kayser, M. 2010. The human genetic history of Oceania: near and remote views of dispersal. *Curr. Biol.* 20: R194–201.

Kilian, M., K. Poulsen, T. Blomqvist et al. 2008. Evolution of Streptococcus pneumoniae and its close commensal relatives. *PloS one* 3: e2683.

Kilian, M., D. R. Riley, A. Jensen et al. 2014. Parallel evolution of Streptococcus pneumoniae and Streptococcus mitis to pathogenic and mutualistic lifestyles. *MBio.* 5: e01490–14.

Kiyono, H., S. Fukuyama. 2004. NALT- versus Peyer's-patch-mediated mucosal immunity. *Nat. Rev. Immunol.* 4: 699–710.

Koch, A., P. Sorensen, P. Homoe et al. 2002. Population-based study of acute respiratory infections in children, Greenland. *Emerg. Infect. Dis.* 8: 586–93.

Krantz, G. S. 1963. The functional significance of the mastoid process in man. *Am. J. Phys. Anthropol.* 21: 591–93.

Kurokawa, H., R. L. Goode. 1995. Sound pressure gain produced by the human middle ear. *Otolanryng. Head. Neck.* 113: 349–55.

Kvaerner, K. J., K. Tambs, J. R. Harris et al. 1996. Otitis media: relationship to tonsillitis, sinusitis and atopic diseases. *Int. J. Pediatr. Otorhi.* 35: 127–41.

Kvestad, E., K. J. Kvaerner, E. Roysamb et al. 2006. Recurrent otitis media and tonsillitis: common disease predisposition. *Int. J. Pediatr. Otorhi.* 70: 1561–8.

Lang, R. W., Y. S. Liu, D. J. Lim et al. 1976. Antimicrobial factors and bacterial correlation in chronic otitis media with effusion. *Ann. Oto. Rhinol. Laryn.* 85: 145–51.

Le Monnier, A., A. Jamet, E. Carbonnelle et al. 2008. Fusobacterium necrophorum middle ear infections in children and related complications: report of 25 cases and literature review. *Pediatr. Infect. Dis. J.* 27: 613–7.

Leach, A. J., J. B. Boswell, V. Asche et al. 1994. Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. *Pediatr. Infect. Dis. J.* 13: 983–9.

Leroi, A. M., A. Bartke, G. De Benedictis et al. 2005. What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? *Mech. Ageing Dev.* 126: 421–9.

Li, H., R. Durbin. 2011. Inference of human population history from individual whole-genome sequences. *Nature* 475: 493–6.

Lildholdt, T., J. Courtois, B. Kortholm et al. 1979. The correlation between negative middle ear pressure and the corresponding conductive hearing loss in children. A 12-month study of 352 unselected 7-year-old children. *Scand. Audiol.* 8: 117–20.

Lim, D. J., Y. M. Chun, H. Y. Lee et al. 2000. Cell biology of tubotympanum in relation to pathogenesis of otitis media - a review. *Vaccine* 19 Suppl 1: S17–25.

Lim, D. J., D. M. Lewis, J. L. Schram et al. 1979. Otitis media with effusion. Cytological and microbiological correlates. *Archiv. Otolaryngol.* 105: 404–12.

Ling, D., R. H. McCoy, E. D. Levinson. 1969. The incidence of middle ear disease and its educational implications among Baffin Island Eskimo children. *Can. J. Public Health* 60: 385–90.

Linz, B., F. Balloux, Y. Moodley et al. 2007. An African origin for the intimate association between humans and Helicobacter pylori. *Nature* 445: 915–8.

Liu, Y. S., R. Lang, D. J. Lim et al. 1976. Microorganisms in chronic otitis media with effusion. *Ann. Oto. Rhinol. Laryn.* 85: 245–9.

Liu, Y. S., D. J. Lim, R. W. Lang et al. 1975. Chronic middle ear effusions. Immunochemical and bacteriological investigations. *Archiv. Otolaryngol.* 101: 278–86.

Lowther, S. A., D. K. Shay, R. C. Holman et al. 2000. Bronchiolitis-associated hospitalizations among American Indian and Alaska Native children. *Pediatr. Infect. Dis. J.* 19: 11–7.

Manica, A., W. Amos, F. Balloux et al. 2007. The effect of ancient population bottlenecks on human phenotypic variation. *Nature* 448: 346–8.

Marchisio, P., L. Claut, A. Rognoni et al. 2003. Differences in nasopharyngeal bacterial flora in children with nonsevere recurrent acute otitis media and chronic otitis media with effusion: implications for management. *Pediatr. Infect. Dis. J.* 22: 262–8.

Margolis, R. H., L. L. Hunter, G. S. Giebink. 1994. Tympanometric evaluation of middle ear function in children with otitis media. *Ann. Otol. Rhinol. Laryngol. Suppl.* 163: 34–8.

Matzinger, P., T. Kamala. 2011. Tissue-based class control: the other side of tolerance. *Nat. Rev. Immunol.* 11: 221–30.

Maughan, H., R. J. Redfield. 2009. Tracing the evolution of competence in Haemophilus influenzae. *PloS one* 4: e5854.

Maynard, J. E., J. K. Fleshman, C. F. Tschopp. 1972. Otitis media in Alaskan Eskimo children. Prospective evaluation of chemoprophylaxis. *JAMA* 219: 597–9.

McEvoy, B. P., J. M. Lind, E. T. Wang et al. 2010. Whole-genome genetic diversity in a sample of Australians with deep Aboriginal ancestry. *Am. J. Hum. Genet.* 87: 297–305.

Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature* 454: 428–35.

Meissner, H. C. 2003. Selected populations at increased risk from respiratory syncytial virus infection. *Pediatr. Infect. Dis. J.* 22: S40–4; discussion S44–5.

Miller, M. R., A. White, M. Boots. 2005. The evolution of host resistance: tolerance and control as distinct strategies. *J. Theor. Biol.* 236: 198–207.

Miller, M. R., A. White, M. Boots. 2007. Host life span and the evolution of resistance characteristics. *Evolution* 61: 2–14.

Monasta, L., L. Ronfani, F. Marchetti et al. 2012. Burden of disease caused by otitis media: systematic review and global estimates. *PloS one* 7: e36226.

Montgomery, P. Q., H. O. L. William, N. Reading et al. 1994. An assessment of the temporal bone lesions of the Broken Hill cranium. *J. Archaeol. Sci.* 21: 331–37.

Moore, H., D. Burgner, K. Carville et al. 2007. Diverging trends for lower respiratory infections in non-Aboriginal and Aboriginal children. *J. Paediatr. Child. Health.* 43: 451–7.

Morris, P. S., A. J. Leach, P. Silberberg et al. 2005. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. *BMC Pediatr.* 5: 27.

Muehlenbein, M. P., J. L. Hirschtick, J. Z. Bonner et al. 2010. Toward quantifying the usage costs of human immunity: Altered metabolic rates and hormone levels during acute immune activation in men. *Am. J. Hum. Biol.* 22: 546–56.

Mulligan, C. J., K. Hunley, S. Cole et al. 2004. Population genetics, history, and health patterns in native americans. *Annu. Rev. Genomics Hum. Genet.* 5: 295–315.

Murphy, K., P. Travers, M. Walport. 2008. *Janeway's Immunobiology*. Abingdon: Garland Science.

Murphy, T. F., L. O. Bakaletz, P. R. Smeesters. 2009. Microbial interactions in the respiratory tract. *Pediatr. Infect. Dis. J.* 28: S121–6.

Murray, C. J. L., A. D. Lopez. 1996. Deaths by age, sex and cause (thousands) 1990 In *Global Burden of Disease*, ed. Murray, C. J. L., A. D. Lopez, pp. 433–68. Geneva: World Health Organization.

Nish, S., R. Medzhitov. 2011. Host defense pathways: role of redundancy and compensation in infectious disease phenotypes. *Immunity* 34: 629–36.

Palva, T., T. Lehtinen, H. Virtanen. 1983. Immune complexes in the middle ear fluid and adenoid tissue in chronic secretory otitis media. *Acta Otolaryngol.* 95: 539–43.

Park, C. H., M. D. Kogan, M. D. Overpeck et al. 2002. Black-white differences in health care utilization among US children with frequent ear infections. *Pediatrics* 109: E84–4.

Park, C. W., J. H. Han, J. H. Jeong, et al. 2004. Detection rates of bacteria in chronic otitis media with effusion in children. *J. Korean Med. Sci.* 19: 735–8.

Peck, A. J., R. C. Holman, A. T. Curns et al. 2005. Lower respiratory tract infections among american Indian and Alaska Native children and the general population of U.S. Children. *Pediatr. Infect. Dis. J.* 24: 342–51.

Pedersen, C. B., B. Zachau-Christiansen. 1986. Otitis media in Greenland children: acute, chronic and secretory otitis media in three- to eight-year-olds. *J. Otolaryngol.* 15: 332–5.

Petrova, P., S. Freeman, H. Sohmer H. 2006. The effects of positive and negative middle ear pressures on auditory threshold. *Otol. Neurotol.* 27: 734–8.

Pichichero, M. E. 2000. Recurrent and persistent otitis media. *Pediatr. Infect. Dis. J.* 19: 911–6.

Prellner, K., P. Christensen, B. Hovelius et al. 1984a. Nasopharyngeal carriage of bacteria in otitis-prone and non-otitis-prone children in day-care centres. *Acta Otolaryngol.* 98: 343–50.

Prellner, K., O. Kalm, F. K. Pedersen. 1984b. Pneumococcal antibodies and complement during and after periods of recurrent otitis. *Int. J. Pediatr. Otorhi.* 7: 39–49.

Read, A. W., J. Gibbins, F. J. Stanley. 1996. Hospital admissions for lower respiratory tract illness before the age of two years in western Australia. *Paediatr. Perinat. Epidemiol.* 10: 175–85.

Real, L. A., R. Biek. 2007. Spatial dynamics and genetics of infectious diseases on heterogeneous landscapes. *J. R. Soc. Interface* 4: 935–48.

Reed, D., S. Struve, J. E. Maynard. 1967. Otitis media and hearing deficiency among Eskimo children: a cohort study. *Am. J. Public Health Nations Health* 57: 1657–62.

Roberts, J. E., R. M. Rosenfeld, S. A. Zeisel. 2004. Otitis media and speech and language: a meta-analysis of prospective studies. *Pediatrics* 113: e238–48.

Rosenfeld, R. M. 2000. Surgical prevention of otitis media. *Vaccine* 19 Suppl 1: S134–9.

Rothstein, J., R. Heazlewood, M. Fraser. 2007. Health of Aboriginal and Torres Strait Islander children in remote Far North Queensland: findings of the Paediatric Outreach Service. *Med. J. Australia* 186: 519–21.

Rovers, M., M. Haggard, M. Gannon et al. 2002. Heritability of symptom domains in otitis media: a longitudinal study of 1,373 twin pairs. *Am. J. Epidemiol.* 155: 958–64.

Ruddle, N. H., E. M. Akirav. 2009. Secondary lymphoid organs: responding to genetic and environmental cues in ontogeny and the immune response. *J. Immunol.* 183: 2205–12.

Rye, M. S., J. M. Blackwell, S. E. Jamieson. 2012. Genetic susceptibility to otitis media in childhood. *The Laryngoscope* 122: 665–75.

Rynnel-Dagoo, B., K. Agren. 2000. The nasopharynx and the middle ear. Inflammatory reactions in middle ear disease. *Vaccine* 19 Suppl 1: S26–31.

Sade, J., A. Ar. 1997. Middle ear and auditory tube: middle ear clearance, gas exchange, and pressure regulation. *Otolanryng. Head. Neck.* 116: 499–524.

Schluger, N. 2010. The Acute Respiratory Infections Atlas, World Lung Foundation, New York.

Schmid-Hempel, P. 2003. Variation in immune defence as a question of evolutionary ecology. *Proc. Biol. Sci.* 270: 357–66.

Schulenburg, H., J. Kurtz, Y. Moret et al. 2009. Introduction. Ecological immunology. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 364: 3–14.

Serhan, C. N., S. D. Brain, C. D. Buckley et al. 2007. Resolution of inflammation: state of the art, definitions and terms. *FASEB J.* 21: 325–32.

Sheldon, B. C., S. Verhulst. 1996. Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. *Trends Ecol. Evol.* 11: 317–21.

Shimizu, T., T. Harada, Y. Majima et al. 1988. Bactericidal activity of middle ear effusion on a single isolate of non-typable Haemophilus influenzae. *Int. J. Pediatr. Otorhi.* 16: 211–7.

Siirala, U., E. A. Lahikainen. 1952. Some observations on the bacteriostatic effect of the exudate in otitis media. *Acta Otolaryngol. (Suppl)* 100: 20–25.

Singleton, R. J., R. C. Holman, R. Plant et al. 2009. Trends in otitis media and myringtomy with tube placement among American Indian/Alaska native children and the US general population of children. *Pediatr. Infect. Dis. J.* 28: 102–7.

Smith, D. F., E. F. Boss. 2010. Racial/ethnic and socioeconomic disparities in the prevalence and treatment of otitis media in children in the United States. *The Laryngoscope* 120: 2306–12.

Smith-Vaughan, H., R. Byun, M. Nadkarni et al. 2006. Measuring nasal bacterial load and its association with otitis media. *BMC ear, nose, and throat disorders* 6: 10.

Stanhope, J. M., W. R. Aitchison, J. C. Swindells et al. 1978. Ear disease in rural New Zealand school children. *NZ Med. J.* 88: 5–8.

Stenfors, L. E., S. Raisanen. 1992. Abundant attachment of bacteria to nasopharyngeal epithelium in otitis-prone children. *J. Infect. Dis.* 165: 1148–50.

Stenfors, L. E., S. Raisanen S. 1993. Secretory IgA-, IgG- and C3b-coated bacteria in the nasopharynx of otitis-prone and non-otitis-prone children. *Acta Otolaryngol.* 113: 191–5.

Stenstrom, C., L. Ingvarsson. 1994. General illness and need of medical care in otitis prone children. *Int. J. Pediatr. Otorhi.* 29: 23–32.

Strugnell, R. A., O. L. Wijburg. 2010. The role of secretory antibodies in infection immunity. *Nat. Rev. Microbiol.* 8: 656–67.

Takahashi, H. 2001. *The Middle Ear: The Role of Ventilation in Disease and Surgery*. Tokyo: Springer-Verlag.

Tamm, E., T. Kivisild, M. Reidla et al. 2007. Beringian standstill and spread of Native American founders. *PloS one* 2: e829.

Teele, D. W., J. O. Klein, B. Rosner. 1989. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J. Infect. Dis.* 160: 83–94.

Tonnaer, E. L., G. T. Rijkers, J. F. Meis et al. 2005. Genetic relatedness between pneumococcal populations originating from the nasopharynx, adenoid, and tympanic cavity of children with otitis media. *J. Clin. Microbiol.* 43: 3140–4.

Tukuitonga, C. R., S. Bell, E. Robinson. 2000. Hospial admission among Pacific children Auckland 1992–97. *NZ Med. J.* 113: 358–61.

Turner, D., E. Leibovitz, A. Aran et al. 2002. Acute otitis media in infants younger than two months of age: microbiology, clinical presentation and therapeutic approach. *Pediatr. Infect. Dis. J.* 21: 669–74.

Van Dyke, A. L., M. L. Cote, A. S. Wenzlaff et al. 2009. Cytokine SNPs: Comparison of allele frequencies by race and implications for future studies. *Cytokine* 46: 236–44.

Vernacchio, L., S. M. Lesko, R. M. Vezina et al. 2004. Racial/ethnic disparities in the diagnosis of otitis media in infancy. *Int. J. Pediatr. Otorhi.* 68: 795–804.

Watson, K., K. Carville, J. Bowman et al. 2006. Upper respiratory tract bacterial carriage in Aboriginal and non-Aboriginal children in a semi-arid area of Western Australia. *Pediatr. Infect. Dis. J.* 25: 782–90.

Wells, C. A., T. Ravasi, D. A. Hume. 2005. Inflammation suppressor genes: please switch out all the lights. *J. Leukoc. Biol.* 78: 9–13.

Westerberg, B. D., F. K. Kozak, E. E. Thomas et al. 2008. Is the Healthy Middle Ear a Normally Sterile Site? *Otol. Neurotol.*

WHO. 2004. Chronic suppurative otitis media: Burden of Illness and Management Options, World Health Organisation, Geneva.

Wiet, R. J., W. J. Doyle, T. R. Gest et al. 1982. An interracial study of the morphometrics of the skull base with reference to the Eustachian tube In *Cholesteatoma and Mastoid Surgery. Proceedings of the 2nd Conference.*, ed. J Sade. Amsterdam: Kugler.

Williams, C. J., H. L. Coates, E. M. Pascoe et al. 2009. Middle ear disease in Aboriginal children in Perth: analysis of hearing screening data, 1998–2004. *Med. J. Australia* 190: 598–600.

Williams, P., M. Gracey, P. Smith. 1997. Hospitalization of aboriginal and non-aboriginal patients for respiratory tract diseases in Western Australia, 1988–1993. *Int. J. Epidemiol.* 26: 797–805.

Wilson, M. 2005. *Microbial Inhabitants of Humans*. Cambridge: Cambridge University Press.

Wirth, T., A. Meyer, M. Achtman. 2005. Deciphering host migrations and origins by means of their microbes. *Mol. Ecol.* 14: 3289–306.

Wirth, T, G. Morelli, B. Kusecek et al. 2007. The rise and spread of a new pathogen: seroresistant Moraxella catarrhalis. *Genome Res.* 17: 1647–56.

Wu, H. Y., M. W. Russell. 1997. Nasal lymphoid tissue, intranasal immunization, and compartmentalization of the common mucosal immune system. *Immunol. Res.* 16: 187–201.

Yamanaka, N., H. Faden. 1993. Antibody response to outer membrane protein of nontypeable Haemophilus influenzae in otitis-prone children. *J. Pediatr.* 122: 212–8.

Yamaoka, Y. 2009. Helicobacter pylori typing as a tool for tracking human migration. *Clin. Microbiol. Infect.* 15: 829–34.

Young, M., K. Kandola, R. Mitchell et al. 2007. Hospital admission rates for lower respiratory tract infections in infants in the Northwest Territories and the Kitikmeot region of Nunavut between 2000 and 2004. *Paediatr. Child Health* 12: 563–6.

Zonis, R. D. 1968. Chronic otitis media in the southwestern American Indian. I. Prevalence. *Archiv Otolaryngol* 88: 360–5.

Table

Summary of published data documenting increased prevalence of otitis media in the Native American, Inuit, Maori, and Australian Aborigine indigenous groups. Note that, for comparison, the prevalence of CSOM in white children in a developed world environment is estimated at less than 1% (Bhutta 2014). References for data: a) Curns et al, 2002; b) Singleton et al, 2009; c) Pedersen and Zachau-Christiansen, 1986; d) Maynard et al, 1972; e) Zonis, 1968; f) Gribben et al, 2012; g) Giles and Asher, 1991; h) Hamilton et al, 1980, i) Boswell and Nienhuys, 1995; j) Morris et al 1995; k) Williams et al, 2009; l) Gunasekera et al, 2007; m) Rothstein et al 2007. For the Aborigine Australian, also see the review by Jervis-Bardy et al (2014).

	Epidemiology of AOM	Epidemiology of CSOM
Inuit	Hospital presentation in children is 1.5 to 3 times higher than in other populations[a, b]	Prevalence of 6–30% in children[c,d]
Native American		Prevalence of 6–30% in children[e]
Maori	No difference in incidence reported[f]	Prevalence of 3–10% in children[g,h]
Aborigine Australian	Rate of AOM/OME in infancy is 3 times higher than in other populations[i]	Prevalence of 15% in infants[j], 2% in older children[k]. 4–5 times more common that in non-indigenous populations[l, m]

Figure 1: The middle ear is an air-filled cleft (shaded pink). Anatomically it is divided into the Eustachian tube, the tympanic cavity, and the mastoid air cell system. Functionally it is partitioned into an immune defence function in the antero-inferior portion, and a trans-mucosal gas exchange function in the postero-superior portion.

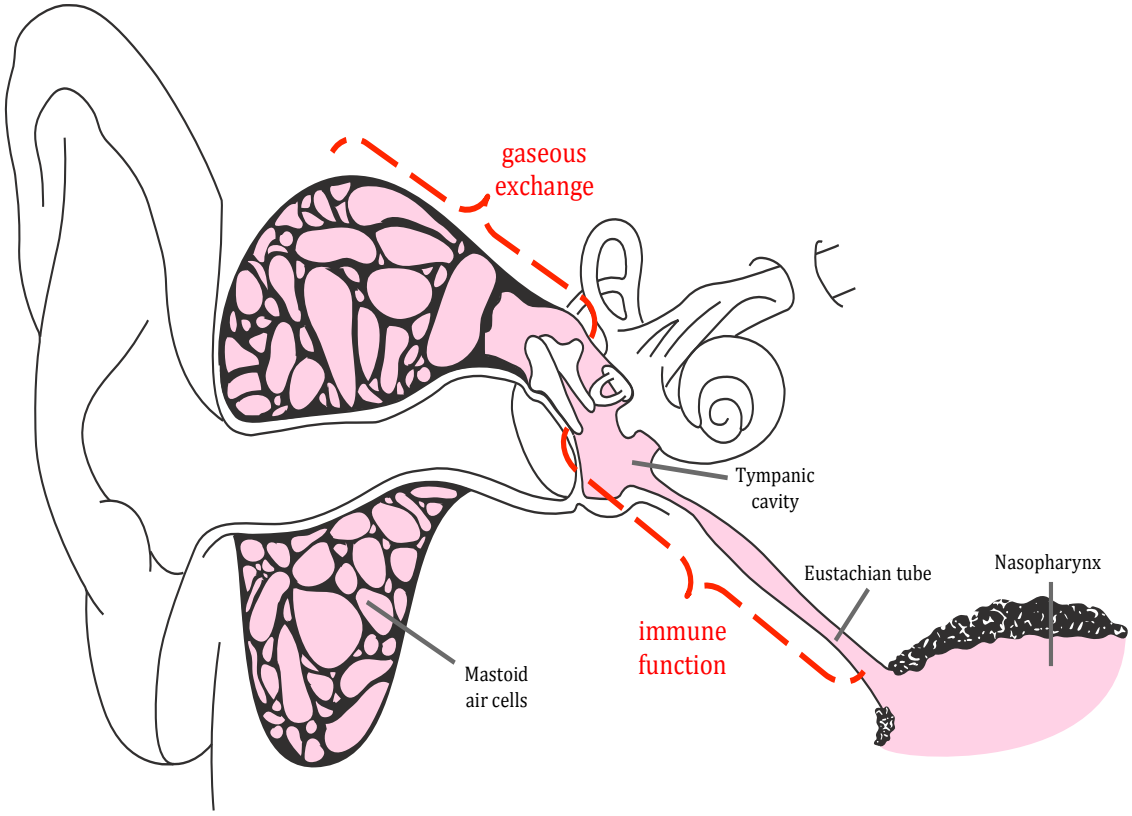

Figure 2: Genera found on metagenomic analysis of the nasopharynx microbiome of 18-month old infants. Adapted from Bogaert et al, 2011.

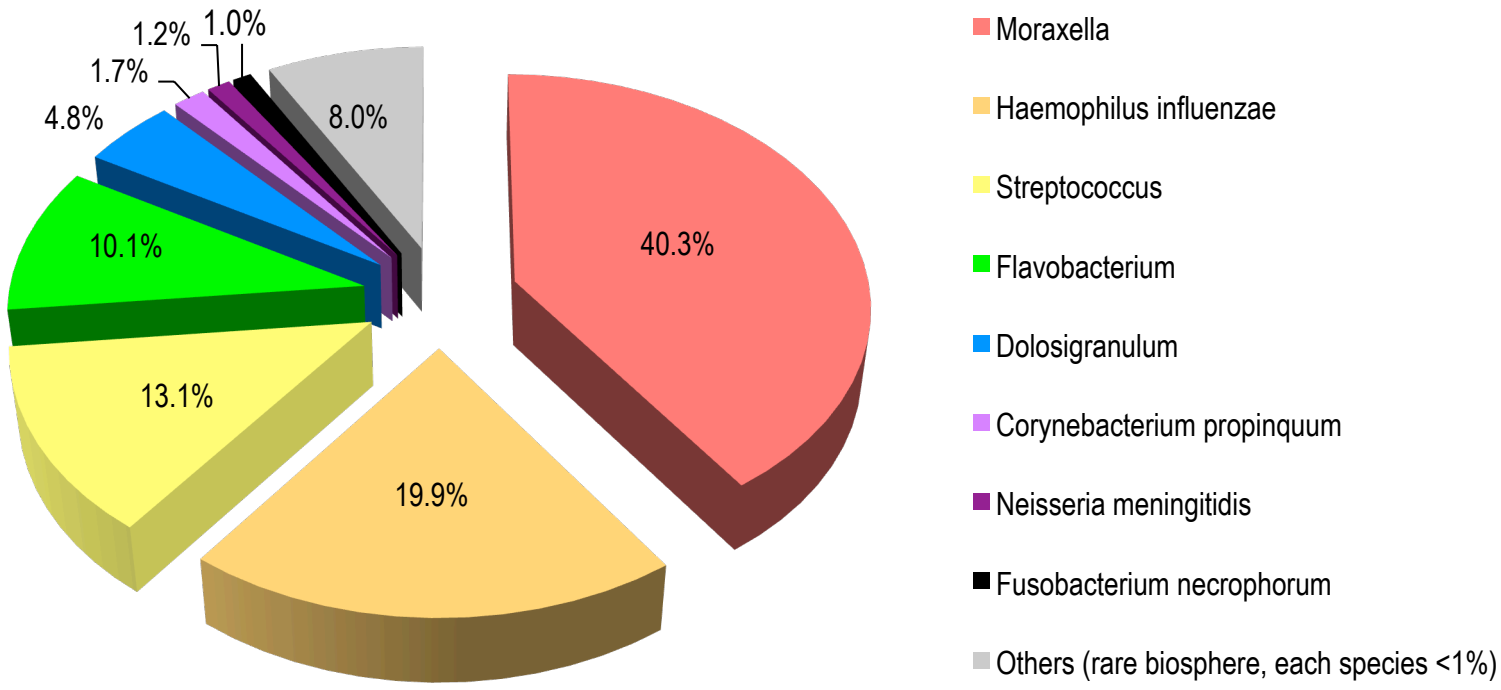

Figure 3: Nasal Associated Lymphatic Tissue (NALT) as a component of the immune system. Artwork adapted from *Toronto Notes* (Chen & Tran 2011).

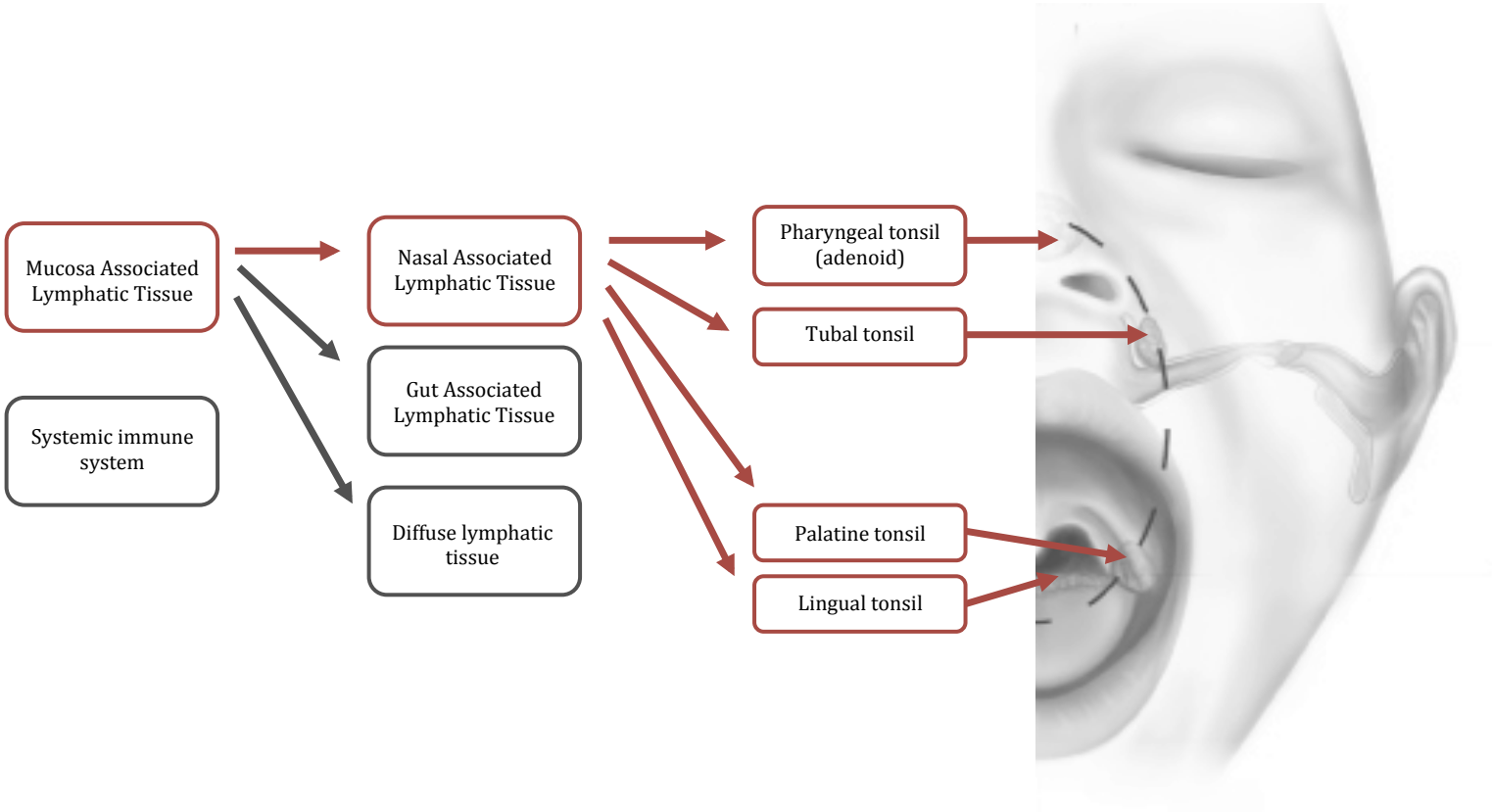

Figure 4. A simplified map of human population migrations prior to onset of European world colonization (c.500 years ago). Annotations are focused on populations known to have a high contemporary incidence of OM. Data derived from a number of sources (Gibbard & van Kolfschoten 2004, Kayser 2010, McEvoy et al 2010, Mulligan et al 2004, Tamm et al 2007).